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Incidence of medication-related harm in older adults following hospital discharge: A systematic review

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Abstract

Objectives To determine the incidence, severity, preventability and risk factors for medication-related harm (MRH) in community-dwelling older adults following hospital discharge.

Design Systematic review

Setting A search of Medline, EMBASE, CINAHL, and the Cochrane Library was undertaken without time restrictions

Participants Older adults (average age ≥65 years) participating in observational studies investigating adverse drug reactions (ADR) or adverse drug events (ADE) post-discharge within a defined follow-up period

Measurements The abstracts of all articles were initially screened by one author to exclude obviously irrelevant articles. The remaining articles were independently screened by two authors for inclusion. Data extraction, including study characteristics, MRH incidence and risk factors, and, critical appraisal was performed by two authors independently, and verified by a third reviewer. Disagreements were resolved through discussion.

Results Out of 584 potentially relevant articles, eight studies met our inclusion criteria; five North American and three European. Most of the included studies were of moderate quality. There was a wide range in MRH incidence, from 0.4% to 51.2% of patients, and 35% to 59% of MRH was preventable. The MRH incidence within 30 days post-discharge ranges from 167 to 500 events per 1000 patients discharged (17-51% of patients). Substantial methodological heterogeneity exists across multiple domains of the studies, including ADR and ADE definitions, characteristics of recruited populations, the follow-up duration post-discharge, and data collection.

Conclusions Medication-related harm is common following hospital discharge in older adults. However, a clear understanding of the epidemiology is hampered by methodological inconsistencies between studies and a paucity of data on risk factors. There is need for international consensus on conducting and reporting MRH studies. Data from large, multicentre studies examining a range of biopsychosocial risk factors could add insight to this important area of patient safety.

Key Words Systematic review, older adults, medication harm, hospital discharge, epidemiology

Introduction

Reducing severe, avoidable medication-related harm (MRH) by 50% over the next five years is the World Health Organisation's third global patient safety challenge [1]. The MRH experienced by patients is often described in terms of (1) adverse drug reactions (ADR), where patients experience a noxious and unintended reaction caused by a medicine at appropriate dosage, or, (2) adverse drug events (ADE) which includes an ADR or an injury related to medicine use at inappropriate dosage (e.g. a medical error) [2–7]. In this paper, ADR and ADE is discussed as 'medication-related harm' (MRH), in accordance with recent World Health Organisation (WHO) terminology[1].

Older adults (≥ 65 years) are a particularly high-risk population for MRH due to polypharmacy [8] and age-related pharmacokinetic and pharmacodynamics changes. [9] Approximately 10% of hospital admissions of older adults are attributable to MRH [10], and the incidence of MRH is increasing in Europe and the United States (US) [11–14]; between 2005/6 to 2013/14 the rate of US emergency department visits for MRH almost doubled from 5.2 to 9.7 visits per 1000 older adults. Excess healthcare cost in the US due to a preventable MRH event to a community-dwelling older adult has been estimated at $2000.[15]

Reducing MRH during transitions of care is a priority area in the WHO's global challenge[16]. Patients and carers describe the transition period around hospital discharge as posing a unique, high risk situation for the occurrence of MRH[17–19]. During this period, patient deconditioning from hospitalisation alongside ongoing recovery from illness [20] is compounded with frequent confusion and inaccuracies in medicines management. Medication discrepancies affect up to one in two older patients around hospital discharge [21], and can be compounded with administrative difficulties receiving medicines and poor patient education of medicines use [22]. Coordination following hospital discharge between secondary care, primary care, and patients and carers, is commonly inadequate. Based on four studies from the US and Australia, a recent systematic review found that 5%-38% of discharge summaries are never received by primary care physicians [23]. The quality of information communicated is also problematic. For instance, the same review found that 40% of discharge summaries did not provide diagnostic test results, 75% no information on

pending tests, 22% lacked information on discharge medications and 58% did not communicate follow-up plans.

A review of medication problems experienced by older adults around hospital discharge was conducted almost a decade ago[24]. Fourteen studies of medication problems in community and care home settings, including medication discrepancies, education, non-adherence, drug interactions and MRH, were identified. The authors could not estimate the magnitude of the problem due to study heterogeneity. In the meantime, despite no systematic quantification of the problem, there have been numerous interventional studies to reduce MRH in the post-discharge period [25,26]. In view of this we conducted a systematic review to specifically investigate the epidemiology of MRH, in contrast to all medication problems which may or may not manifest in patient harm. Our aim was to determine the incidence, severity, preventability and risk factors for MRH in community-dwelling older adults post-discharge.

Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Table S1) in conjunction with the Joanna Briggs Institute methodological guidance for systematic reviews of observational epidemiological studies[27]. Our primary objective was to provide a synthesis of the epidemiological data on MRH in community-dwelling older adults following hospital discharge.

Search strategy

Two authors (NP and TR) initially conducted an electronic search of Medline, EMBASE, CINAHL, and the Cochrane Library, from their inception to June 2016 without restrictions. We re-ran this search in June 2017 looking for any new studies. The search strategy was designed in Medline (using the Healthcare Databases Advanced Search from the National Institute of Health and Care Excellence) using a combination of key words and Medical Subject Headings (MeSH) (Table S2). We subsequently adapted this search strategy for EMBASE and CINAHL. Key concepts in the search strategy were ‘adverse drug reaction’,

'elderly' and 'hospital discharge'. For each of these concepts, synonyms, related terms and controlled vocabulary terms were selected and combined using Boolean and proximity operators, and truncation, to ensure alternative forms were retrieved. In addition to this, reference lists of relevant articles were scanned to identify any articles not found in the electronic search. We also consulted the studies in a review published in 2010 on a similar theme[24], conducted forward citation searches on this prior review and on studies that we identified for inclusion, and successfully corresponded with investigators of four included studies to ensure we did not miss any articles.

Selection criteria

We considered all published observational studies that evaluated MRH (ADR or ADE) to community-dwelling older adults (average age ≥65 years) within a defined follow-up period after hospital discharge. We included studies where the incidence or prevalence of MRH was reported or could be calculated. Given our objective was to establish the extent of MRH is the general older population discharged from hospital, we had the following exclusion criteria; (1) studies investigating only re-hospitalized patients, (2) studies only investigating patients with a specific disease, condition, or harms of one particular medicine, (3) studies of institutionalized patients.

Outcomes

Our primary outcome of interest was the incidence of MRH post-discharge. Secondary outcomes included the proportion of serious events, preventable events, and associated risk factors.

Study selection

The titles and abstracts of identified articles were screened by one author (NP) to exclude obviously irrelevant articles (n=338). The remaining papers (n=215) were independently screened by two authors (NP and AP), excluding those identified as reviews, interventional studies, conference proceedings, research letters and protocol papers, articles related to a specific medicine or condition, or, not investigating the period post-hospital discharge. Full-text articles of potentially eligible titles and abstracts were independently reviewed by the same two authors and selected according to inclusion criteria. These studies were then

reviewed by a third author (KA) to confirm their eligibility for inclusion. Any disagreement was resolved through discussion.

Data extraction

Data extraction was performed independently by two reviewers (NP and AP) onto a standard data collection form (Table S3), and verified by a third reviewer (KA). We extracted the following data from included articles: study year and country, study design, discharge setting, duration of follow-up, methods used for data collection and causality assessment, ADE and ADR incidence or prevalence, severity, preventability, and, associated risk factors.

Quality assessment

Two authors (NP and AP) independently assessed the quality of included studies using the Joanna Briggs Institute critical appraisal tool for prevalence studies [27]. The nine domains in this tool address sampling bias (target population, sampling, sample size, description of participants and setting), coverage bias (coverage of identified sample), measurement bias (methods to identify outcome, reliability in outcome measurement, appropriate statistical analysis), and, non-response bias (response rate). Where any disagreements arose, these were resolved through discussion. A risk of bias figure was completed for included studies using RevMan Version 5.3.

Data synthesis

We report the incidence proportions of MRH stated in the included studies. In studies where this was not clearly stated, we calculated the incidence proportion from the available data (number of persons that developed MRH / total population at risk). Where the number of events within the population was stated, we additionally calculated the incidence of events per 1000 discharges. We have not reported incidence rates (where follow-up time is incorporated into the denominator) as this would be misleading, given that the risk of MRH following hospital discharge is not constant over time. Data was extracted on the medicine classes commonly implicated in MRH. If this was reported in an alternative format e.g. mixture of medicine classes and specific medicines themselves, we categorised the medicines using the WHO Anatomical Therapeutics Coding system[28].

Results

Study Selection

We identified 584 individual records from our search strategy, out of which we read 31 articles in full as they were deemed relevant based on their title and abstract. From this we excluded 24 articles as they did not meet all the inclusion criteria, and one additional study was identified from a reference list of an article. Therefore, eight observational studies met our inclusion criteria (Figure 1).

Study Characteristics

Study characteristics are outlined in Tables 1 and 2. Five studies were conducted in North America[29–33], and three studies in Europe (Netherlands[34], Croatia[35] and France[36]). All the identified studies were cohort studies (prospective, n=5[29–31,34,35], retrospective, n=2[32,33]), and one which was a prospective population-based study [36]. The number of participants included in the studies ranged from 209 to 7540, and the mean age of patients 67.7 to 80.0 years.

Participant recruitment and follow-up

The recruitment setting varied between studies, with most studies recruiting from general medical wards, however others specified inclusion of patients also from surgical wards[30] and all wards[36]. Most studies excluded patients discharged to a nursing home, those with a terminal illness and patients admitted to psychiatric units. However, one study exclusively recruited patients discharged to receive nursing care at home [31]. Three studies excluded patients with dementia; one excluded all patients with dementia[35], one excluded those with severe dementia[30] and another excluded those with dementia and no home carer [31]. Objective criteria for the diagnosis and severity of dementia were not reported.

The period of follow-up post-hospital discharge was one month in five studies[29,31,33,35,36], whilst the shortest follow-up was two weeks [34] and the longest one year [30]. Half of the studies recruited patients from more than one hospital [30,33,34,36]. A nationwide study of post-discharge ADR from France recruited patients referred to hospital for all causes by their GP, and then followed up only the subset of patients that re-consulted their GP within 30 days of discharge [36].

Definition of MRH

Definitions of MRH varied between studies, and two studies did not report an explicit definition[29,31]. Two studies used a World Health Organisation definition of ADR [35,36], and one used a modification of this to include harm from therapy discontinuation[36] . Another study classified a range of medication problems under ADR including 'unsafe drug for patient, allergic reaction, contraindication present, incorrect administration, clinically relevant drug interaction, undesirable effect' [33]. Two studies reporting ADE had a very similar definition[29,32], however, one of these included harms from patient non-adherence.[32]

Data collection and MRH causality assessment

Data collection was primarily through medical chart reviews [32,33] and in some cases also patient interview; patients were interviewed by telephone [29,30] or in-person [31,34,36] , and in one study the interview was combined with a physical examination of patients[35].

Data was collected by a range of health professionals, including community-based pharmacy technicians [34], to clinical pharmacists [32] and GP [36] to physicians with expertise in clinical pharmacology[35]. Only some studies reported use of a tool to attribute causality to a medicine for a particular harm, and this included the validated Naranjo algorithm [30,31,35] , and an algorithm designed by French experts in pharmacovigilance [36].

Methodological Quality

The results of our critical appraisal of the included studies can be seen in Figure S1. Overall, the literature base was of moderate quality. Our assessment found that in five out of eight studies the sample frame (i.e. recruited cohorts to investigate the target population) was associated with a high risk of bias[30,31,33,34,36]. Quality indices that we assessed to have low risk of bias included the sample size, sampling method, and the methods used to identify MRH.

Incidence of MRH

The incidence proportion of MRH ranged from 0.4% patients within 30 days of discharge [36], in a French study of ADR presenting to primary care post-discharge, to 51.2% over a two-week period post-discharge [34] in a Dutch study reporting 'side-effects' to medicines (Table

3). The incidence of MRH events ranged from 4.0 per 1000 patients over 30 days to 615.1 per 1000 patients over one year of follow-up [30]. The follow-up period in most studies (n=5, 62.5%) was 30 days[29,31,33,35,36]. The MRH incidence within 30 days post-discharge ranged from 167 to 500 events per 1000 patients (17-51% of discharged patients)[29,31,33,35], excluding the very low MRH incidence reported by Letrilliart *et al* (2001) where only patients consulting their GP were followed-up. [36] The substantial methodological variation between studies precludes reliable meta-analysis of the MRH incidence [27].

Severity, preventability and risk factors

Severity of MRH was determined in four studies[30,32,35,36]. Two studies used the same criteria to define serious MRH[35,36]; death, life-threatening, hospitalisation or disability. The proportion of total MRH judged 'serious' ranged from 6.9%[35] to 60% [36] (Table 3). Preventability of MRH was reported in four studies with variable definitions, and ranged from 35% to 59% of MRH[30,32,35,36] (Table 3).

Cardiovascular medicines were the most commonly prescribed drugs at hospital discharge.[31,35] They were implicated in the largest proportion of MRH, associated with 18.8% to 55.7% of events[30–33,35,36]. Anticoagulants were also a commonly implicated drug class, associated with up to 20% of events [36]. Four studies examined the association of risk factors with MRH[30,31,35,36], and three of these studies performed multivariable analysis to identify independent predictors[30,31,35](Table 4). Increasing number of medicines[30,35], new medicines at discharge[31], warfarin[30,35], furosemide[35], lower score on Mini-Mental State Examination for impaired cognition [31] and female gender[31] were independent risk factors for MRH.

Discussion

To our knowledge, this is the first systematic review to describe the epidemiology of medication-related harm in community-dwelling older adults after hospital discharge. We included eight studies reporting a wide range in the incidence of MRH, from 0.4% to 51.2% of patients. We found substantial methodological heterogeneity between studies, including (1) outcome definitions i.e. WHO definition of ADR to no reported definition, (2) the

population cohort recruited i.e. patients with polypharmacy to patients requiring community nursing care, (3) the follow-up period i.e. from 14 days to 365 days, and, (4) the data collection methods i.e. using solely medical records to including patient interviews, and physical examination. Leendertse *et al*'s review in 2010 of medication-related hospitalisations similarly demonstrated major variations in study characteristics resulting in a prevalence range of 0.1% to 54% between identified studies [37]. Our review indicates that a lack of consensus on conducting and reporting MRH research continues to hamper a clear understanding of the burden of MRH.

Our results show that MRH is experienced by a considerable proportion of older adults within 30 days post- discharge. The one-month incidence ranges from 167 to 500 events per 1000 patients (17-51% of patients). This does not include one study that reported an outlying low incidence of MRH (0.4% patients), where only patients that consulted their GP post-discharge were followed-up.[36] This study excluded MRH that resulted in the use of other health services e.g. the emergency department, or self-managed at home, and therefore underreported the magnitude of MRH. Ahmad *et al* (2014) found that half of the discharged patients in their study experienced MRH within two weeks of discharge [34]. This was a high incidence relative to other studies and is likely to reflect the particularly high-risk cohort of polypharmacy patients that were recruited.

Between 35% and 59% of MRH was preventable in the included studies, and this builds on a previous systematic review of MRH in the community (not post-discharge) in all age groups which reported 11-27.5% as preventable [38]. Given the high risk around hospital discharge of medication discrepancies, [39,40] poor communication to patients of medication changes and possible adverse effects, [17,36,41] and deficiencies in information transfer to primary care, [23] the higher proportion of preventable MRH that we report is not a surprise.

None of the included studies considered the financial costs of MRH to healthcare systems. Reducing preventable MRH post-discharge may be an opportunity for financial savings within healthcare systems. An economic analysis of the direct costs from healthcare utilisation attributable to post-discharge MRH within a large, multicentre prospective study

would be a starting point. Currently data on MRH costs are predominantly based on hospital inpatients[42,43]

Our findings highlight the crucial need for consensus in defining MRH, collecting MRH data, ascribing causality and reporting findings. There are multiple definitions for ADR and ADE,[3,5–7] and these can be contradictory. For example, the WHO definition of ADR stipulates 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man' [7](thereby excluding error), whereas the definition by Edwards and Aronson (2000) includes ADR related to alternative doses that might have arisen by error[5]. The common exclusion of MRH due to non-adherence and medical error in ADR studies does not reflect the reality of patient experience[19] or clinical practice[4]. We recommend that future studies identify harm due to non-adherence and medical error alongside ADRs, reporting these separately and collectively under the terminology of 'medication-related harm'. This would align with the WHO's global medication safety initiative [1].

Data collection for MRH studies is more accurate when multiple sources are used[6,44]. Studies that rely solely on medical chart review are likely to underestimate MRH events[44]; patient surveys or interviews are a valuable contribution to MRH data[45,46] and should be routinely captured to generate more robust evidence[47]. Only one study included a medical examination looking for physical signs of MRH, conducted by a physician with clinical pharmacology training.[35] The authors did not report the proportion of MRH that was identified with this unique approach relative to chart reviews and patient reports. However, several patients experiencing statin-induced myopathy and corticosteroid-induced Cushing's syndrome were identified that could have been missed without a clinical examination. The value of the examination will of course depend upon the education and training of the physician conducting it.

Whilst no gold standard exists for ascribing causality when assessing MRH[48], combining an algorithmic approach (e.g. Naranjo[49]) and expert opinion from multiple reviewers is comprehensive and may improve the accuracy of causality judgements[50]. Similar to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[51] formulated by the International Society for Pharmacoeconomics and Outcomes Research, we recommend

an international, multidisciplinary task force (including academia, clinicians, pharmaceutical industry, regulatory authorities, and patient and carer representation[52]) to formulate best practice guidance for investigating and reporting MRH. A Delphi Panel could be organised online, requiring minimal financial support, and is a validated methodology to achieve expert consensus[53].

There is no established time-frame defining the heightened risk of adverse events in the post-discharge period. Five studies (63%) in our review followed-up participants for 30 days. While arbitrary, this is consistent with the 'post-hospital syndrome' describing a 30-day period of heightened vulnerability from ongoing illness recovery and the physiological stresses of hospitalisation, including sleep deprivation, poor nutrition and deconditioning [20]. Kanaan *et al* (2013) investigated a 45 day post-discharge period and found the vast majority of MRH takes place within 30 days [32], whilst Hanlon *et al* (2006) conducted a one-year follow-up and showed that MRH occurred predominantly in the first three months [30]. Some MRH manifests over an extended time-frame e.g. immunosuppression-related sepsis or osteoporotic fracture from extended prednisone use in temporal arteritis. These cases of MRH would likely be missed in a limited follow-up of weeks (or even months), which makes it particularly challenging to propose a specific follow-up period.

There were specific medication-related features that were associated with an increased risk of MRH in more than one study. Increasing number of medicines, a well-established risk factor for MRH in the inpatient setting [54], was an independent predictor of post-discharge MRH in two included studies [30,35]. Our results also highlighted warfarin as a significant risk-factor[30,35], however, the most recent included study by Westberg *et al* (2017) did not find that anticoagulants were a particularly frequent class of drug implicated in MRH[33]. This could reflect changing prescribing patterns of anticoagulant use from vitamin-K antagonists to direct oral anticoagulants, and indications that some direct oral anticoagulants have an improved safety profile over warfarin [55]. Only the study by Gray *et al* (1999) explored the influence of psychosocial factors on the risk of MRH, and found that reducing cognition as measured on mini-mental state examination was significant[31]. None of the studies investigated the role of low health literacy, which is increasingly recognised as a potentially

modifiable determinant of MRH[56]. The influence of other important variables such as frailty, carer support, and socioeconomic status are yet to be explored, and could prove fruitful to increasing our understanding of the pathways underlying MRH.

Our review has several limitations. Although we performed a comprehensive literature search, we could not identify unpublished studies. The heterogeneity of the identified studies precluded a meta-analysis to estimate the incidence of MRH, our primary outcome of interest. Several outcomes of interest, including the severity and preventability of MRH were reported in only a proportion of included studies and mostly not improved through contact with original investigators. Many studies excluded patients with dementia and patients discharged from psychiatric wards. Given the high number of medicines used in these patients, it is important that future studies are designed to include such patient groups.

Conclusions

Medication-related harm is common in older adults following hospital discharge. However, a clear understanding of its epidemiology is hampered by methodological inconsistencies between studies. There is a need for further prospective epidemiological research on this topic to identify key risk factors, and international consensus on conducting and reporting studies investigating MRH.

Conflicts of interest: No personal or financial conflicts of interest of any authors
Author Contributions: NP: conception and design, systematic search, study selection, data extraction, data interpretation, preparation of manuscript. AP: study selection, data extraction, data interpretation, preparation of manuscript. KA: conception and design, study selection, data extraction, data interpretation, preparation of manuscript. TR: systematic search, preparation of manuscript. CR: conception and design, data interpretation, preparation of manuscript.
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Table 1. Characteristics of included studies

Study (Year)	Country	Study design	Recruitment setting	Follow up duration (days)	Participant (number)	Participant age in years (Mean, SD or Median, range)	Population characteristics
Westberg (2017)	USA	Retrospective cohort	Three hospitals. Wards not reported	30	408	67.7+/-13.8	Patients had been pre-selected based on risk profile as requiring medication review in the community. Key exclusions: palliative or neoplasm as primary diagnosis
Ahmad (2014)	Netherlands	Prospective cohort	Eight urban hospitals. All wards except psychiatry and oncology	14	340	76 (range 60-95)	Key exclusions: Patients using less than five long-term medicines; psychiatry or oncology patients; nursing home patients.
Marusic (2014)	Croatia	Prospective cohort	One hospital, one general medical ward	30	209	74 (range 65-89)	Key exclusions: impaired cognition, terminal illness, inability to be followed-up
Kanaan (2013)	USA	Retrospective cohort	One hospital. All wards, except psychiatry	45	1000	78.8 +/-7.1	Key exclusions: Psychiatric patients; discharged to care home
Hanlon (2006)	USA	Prospective cohort	Eleven veteran-affairs hospitals. Medical or surgical wards.	365	808	Not reported. Age categories reported as 53.6% 65-74 years, 46.4% 75 years or over	Key exclusions: nursing home, previously had geriatric specialist input in community or hospital, disabling or terminal disease, severe dementia, unable to come to follow-up clinic visits.
Forster (2004)	Canada	Prospective cohort	One hospital. Medical wards.	30	328	71 (IQR 54-81)	Key exclusions: none reported
Letrilliart (2001)	France	Prospective nationwide	All hospitals serving 305 general practices across France. All wards	30	7540	69 (range not reported)	Patients referred to hospital by participating general practices and then re-consulted within 30 days of hospital discharge. Key exclusions: none reported
Gray (1999)	USA	Prospective cohort	One hospital. Wards not reported.	30	312	80 +/-7.3	Patients receiving home nursing care. Key exclusions: terminally ill, recent MI or CVA, dementia without caregiver at home, non-ambulatory

Definitions: Medication-related harm (MRH), Adverse Drug Reaction (ADR), Adverse Drug Event (ADE), General Practitioner (GP), Standard Deviation (SD), Interquartile range (IQR)
Note that MRH was a sub-category of adverse events in Forster (2004), and a sub-category of drug-related problems in Westberg (2017) and Ahmad (2014).

Table 2: MRH assessment in the included studies

Study (Year)	Study aim	Type of MRH	Definition of MRH	Causality assessment	Data collection method
Westberg (2017)	To describe the number, classification, and severity of drug therapy problems in patients transitioning from hospital to home	ADR	ADR comprised unsafe drug for patient, allergic reaction, contraindication, incorrect administration, clinically relevant drug interaction, undesirable effect	Not reported	Pharmacist initially documents drug-related problem during community medication review and then 3 clinician investigators (one physician, one clinical pharmacist, one resident pharmacist) evaluated the record to attribute clinical significance and likelihood of harm.
Ahmad (2014)	To investigate the occurrence of MRP in discharged patients	ADE	Not reported	Two clinical pharmacologists reviewed information from patient interviews, hospital discharge prescriptions and pharmacy information systems to verify ADE	Semi-structured patient interview by pharmacist technicians.
Marusic (2014)	To evaluate the incidence of ADRs in elderly patients following discharge from an internal medicine clinic	ADR	ADR is one that is noxious, unintended and occurs at a dose normally used in humans	Independent physician review using Naranjo Algorithm.	Follow-up interview and medical examination 30 days post-discharge where physician with clinical pharmacology expertise determined ADR.
Kanaan (2013)	Characterise ADR occurring during post hospitalisation period in older adults	ADE	ADE defined as an injury resulting from a drug, rather than an underlying disease. An ADE can be related to an error or an ADR without an error.	Physician-reviewers considered the sequential relation of drug exposure and event, and whether event was a known potential side-effect	Primary and secondary care medical record review by pharmacists
Hanlon (2006)	To examine the incidence of ADRs in frail elderly persons after hospital discharge	ADR	ADR is one that is noxious, unintended and occurs at a dose normally used in humans*	Blinded geriatric physician/pharmacist reviewer pairs evaluated the ADR narratives prepared by clinical pharmacists using the Naranjo algorithm.	Chart reviews by research nurse and telephone interview by research pharmacist for patient self-report of ADR. Pharmacists then created a narrative of these ADRs.
Forster (2004)	To determine the risk, severity and type of adverse events after discharge	ADE	ADE are the subset of adverse events caused by medications - adverse events are adverse outcomes caused by medical care as opposed to the underlying disease process*	Two physicians reviewed each outcome and determined probability of causality by clinical judgement	Telephone interview with patient by nurse or physician and chart review if readmitted to same hospital
Letrilliart (2001)	To estimate the incidence of post-discharge ADR detected in primary care	ADR	ADR is noxious, unintended and occurs at a dose normally used in humans, but also includes harm occurring from discontinuation of a necessary drug during hospital stay	Combination of medical literature, physician expert judgement and published French algorithm	Teleinformatic data transfer from GP to central information centre based on a standardised protocol
Gray (1999)	To describe the incidence of ADEs within one month post-discharge in elderly patients receiving home health services	ADE	Not reported	Naranjo algorithm	Semi-structured patient interview by trained interviewers

Abbreviations: Medication-related harm (MRH), Adverse Drug Reaction (ADR), Adverse Drug Event (ADE), General Practitioner (GP). *Definitions retrieved from contact with original investigators

Table 3. Incidence, preventability, and, severity of MRH

Study (Year)	Incidence of MRH (events per 1000 patients discharged)	Incidence of MRH in study population, % (follow-up duration)	MRH Preventable, % (definition)	MRH Serious, % (definition)
Westberg (2017)	346	Not reported (30 days)	Not reported	Not reported
Ahmad (2014)	500	51.2 (14 days)	Not reported	Not reported
Marusic (2014)	345	30.1 (30 days)	51.4 (errors that could have been avoided or severity reduced with different actions)	6.9 (fatal, life-threatening, hospitalisation or disability)
Kanaan (2013)	242	18.7 (45 days)	35 (due to error and preventable by any means possible)	24 (clinical judgement)
Hanlon (2006)	615	33 (365 days)	37.6 (prescribing, monitoring, dispensing or adhering errors)	26 (death, hospitalisation, permanent disability, need for intervention to prevent permanent impairment†)
Forster (2004)	167	16.8 (30 days)	Not reported	Not reported
Letrilliart (2001)	4.0	0.4 (30 days)	59 (French algorithm with six criteria*)	60 (fatal, life-threatening, hospitalisation or disability)
Gray (1999)	250	20.3 (30 days)	Not reported	Not reported

*Imbs JL et al. Therapie 1998;53:365-70; † Data retrieved from contact with original investigator

Table 4. Commonly implicated medicines and risk factors associated with MRH

Study (year)	Frequently implicated medicines in MRH (% of events)	Risk factors for MRH examined in study	Independent risk factors of MRH on multivariable analysis
Westberg (2017)	Analgesics (28.4%), Psychotropics & hypnotics (22.7%), Cardiovascular (20.6%)	Not reported	Not reported
Ahmad (2014)	Not reported	Not reported	Not reported
Marusic (2014)	Cardiovascular (40.3%), Anticoagulants (16.7%), Hypoglycaemic agents (13.9%)	Age Gender Number of discharge diagnoses Individual diagnoses (Hypertension, Diabetes, Hyperlipidaemia, Ischaemic heart disease, Atrial fibrillation) Number of medicines* Drug-drug interactions Individual medicines/medicine class (ACE-I, Beta-blockers, Acetylsalicylic acid, Furosemide*, Statins, PPI, Potassium salts, Calcium-channel blockers, Warfarin*)	Number of medicines (≧4), Warfarin, Furosemide
Kanaan (2013)	Cardiovascular (55.7%), Opiates (9.5%)	Not reported	Not reported
Hanlon (2006)	Cardiovascular (27.1%), Anticoagulants (8.6%)	Age Dementia Multiple prescriber* Number of medicines* Comorbidities Renal disease Previous ADR Individual medicines/medicine class (Warfarin*, Theophylline, Anticholinergics, Opioids, Antipsychotics, Benzodiazepines*, NSAIDs*, Tricyclic Antidepressants*, Corticosteroids, Sedatives)	Warfarin, Number of medicines,
Forster (2004)	Not reported	Not reported	Not reported
Letrilliart (2001)	Cardiovascular (26.7%), Anticoagulants (20%)	Age* Gender Type of admission (planned/unplanned) Type of hospital (public/private)	Not reported
Gray (1999)	Cardiovascular (18.8%), Antibiotics (17.2%), CNS (15.6%), Endocrine (15.6%)	Age Gender (Female*) Living alone Alcohol consumption Depression Self-rated health Activities of daily living Cognitive status (MMSE)* Comorbidities Number of medicines Number of new discharge medicines* Medicines increase	Female gender, Number of new discharge medicines, Lower MMSE score

Abbreviations: Central Nervous System (CNS), Ischaemic Heart Disease (IHD), Mini-Mental State Examination (MMSE). *Statistically significant <0.05
In three studies [30,32,35], for consistency, medicines were combined to calculate the proportion due to cardiovascular agents, using the WHO-ATC system

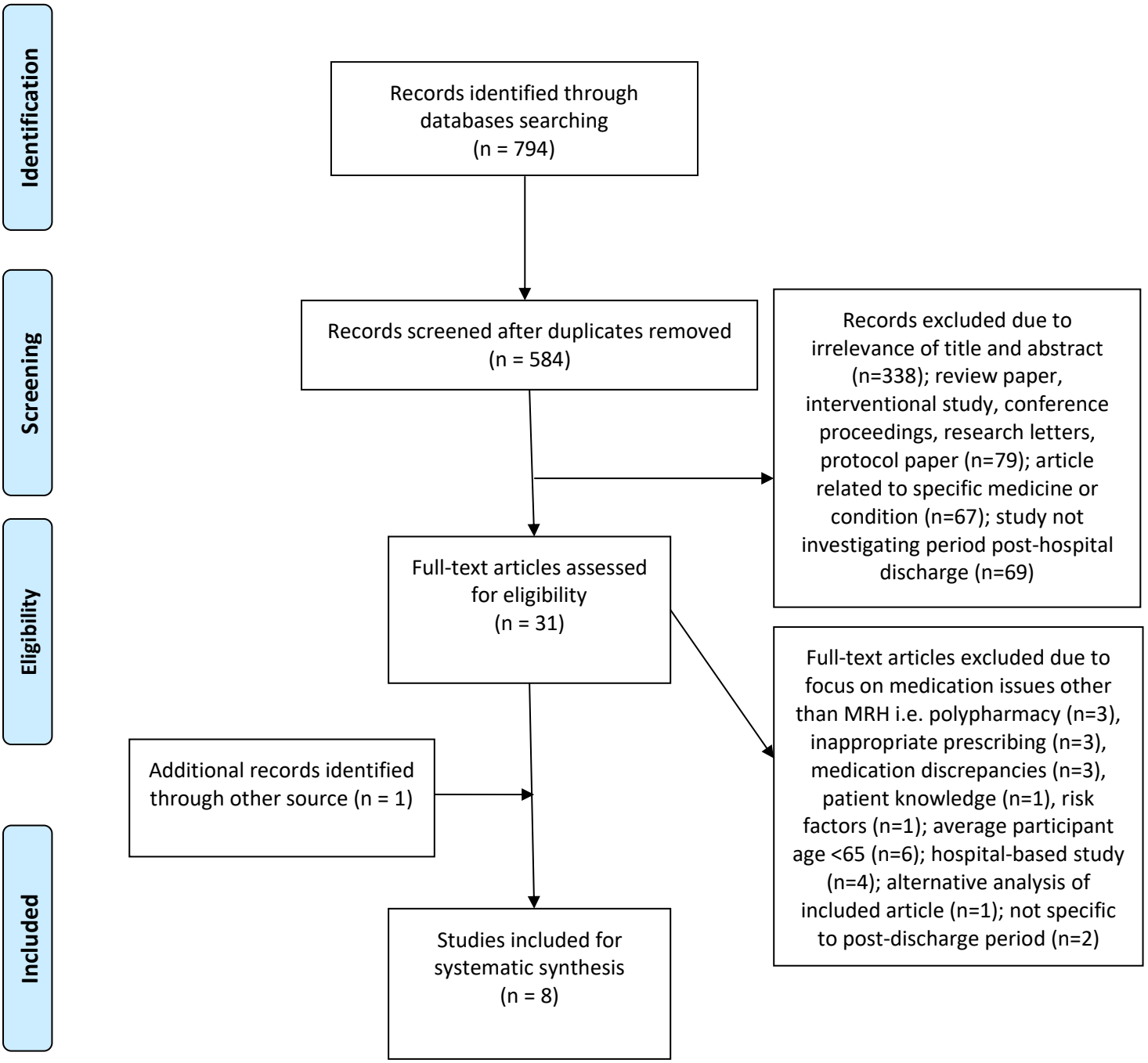
Figure 1. PRISMA flow diagram for included studies

Supplemental Table S1. PRISMA Checklist

Supplemental Table S2. Search strategy designed in Medline

Supplemental Table S3. Data extraction form

Supplemental Figure S1. Risk of bias assessment for included studies


Identification
Screening
Eligibility
Included
Records identified through databases searching (n = 794)
Records screened after duplicates removed (n = 584)
Records excluded due to irrelevance of title and abstract (n=338); review paper, interventional study, conference proceedings, research letters, protocol paper (n=79); article related to specific medicine or condition (n=67); study not investigating period post-hospital discharge (n=69)
Full-text articles assessed for eligibility (n = 31)
Full-text articles excluded due to focus on medication issues other than MRH i.e. polypharmacy (n=3), inappropriate prescribing (n=3), medication discrepancies (n=3), patient knowledge (n=1), risk factors (n=1); average participant age <65 (n=6); hospital-based study (n=4); alternative analysis of included article (n=1); not specific to post-discharge period (n=2)
Additional records identified through other source (n = 1)
Studies included for systematic synthesis (n = 8)

Supplemental Table S1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, Fig 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, Fig 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Supplemental Table S1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6,Fig 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, Tables 1&2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8, Table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

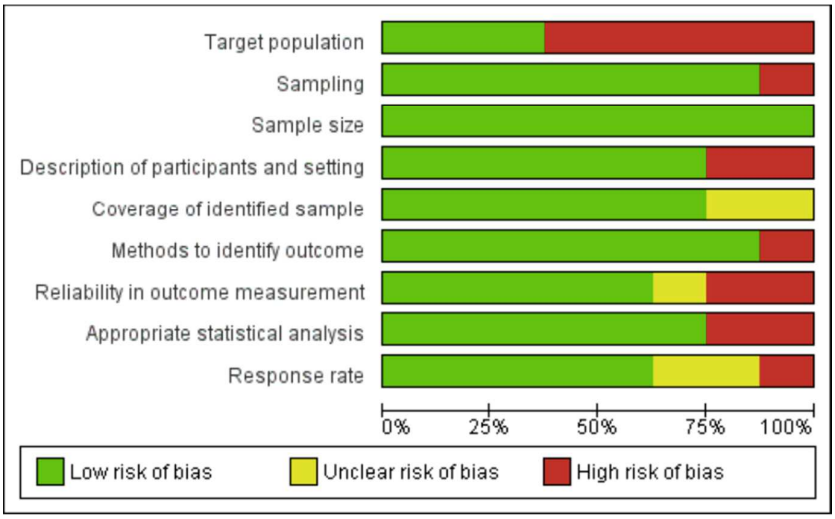
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Table S2. Search Strategy designed in Medline and adapted to other databases

#	Database	Search term	Results
1	Medline	exp *DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS/ep	2837
2	Medline	(((drug* OR medication* OR medicine*) ADJ2 adverse) ADJ2 (effect* OR reaction* OR event* OR problem*)).ti,ab	24362
3	Medline	((drug* OR medication*) ADJ2 (toxicity OR cardiotoxicity OR hepatotoxicity)).ti,ab	12793
4	Medline	(1 OR 2 OR 3)	38659
5	Medline	exp AGED/	2665319
6	Medline	(elder* OR old OR older OR geriatr* OR gerontol* OR aging OR ageing OR senior* OR retiree* OR retired OR "late* life").ti,ab	1486296
7	Medline	(5 OR 6)	3702870
8	Medline	*PATIENT DISCHARGE/	10663
9	Medline	((patient* OR hospital* OR clinic* OR unit*) ADJ3 discharg*).ti,ab	75713
10	Medline	(8 OR 9)	82693
11	Medline	(4 AND 7 AND 10)	232
performed on 01 June 17			

Figure S1. Risk of bias assessment for included studies

A



B

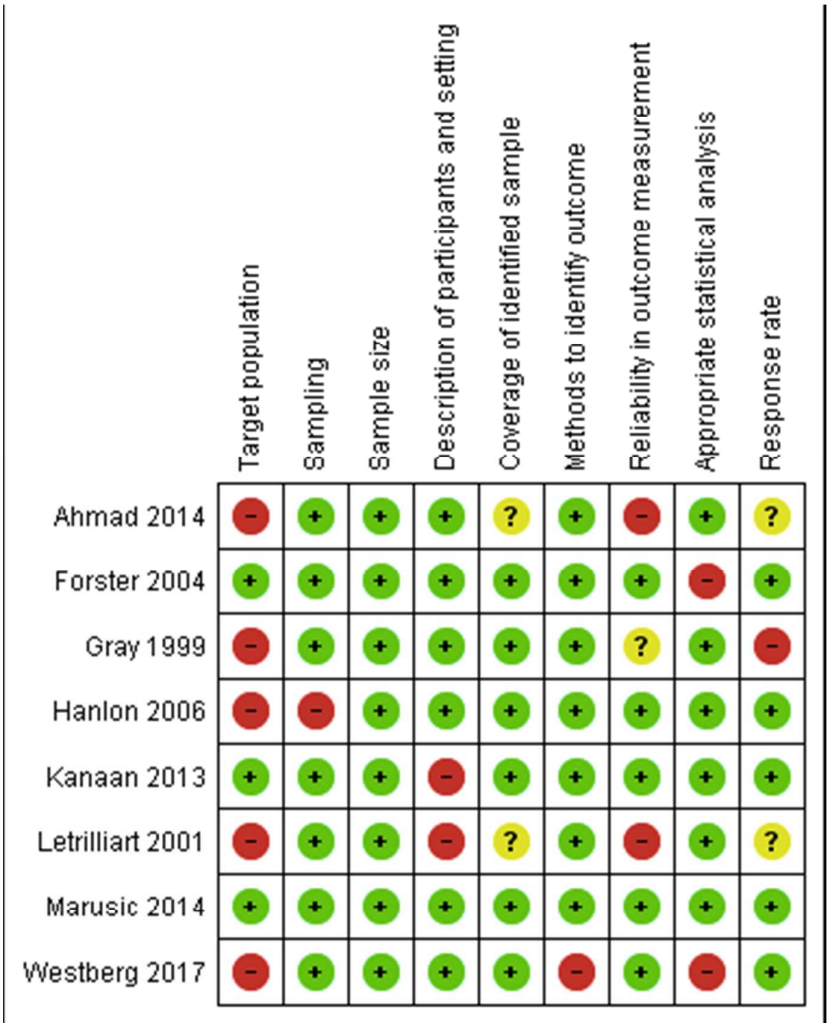


Table S3: Data extraction form

Study Reference:

Methods	Study design: Study aim:
Participants	Number of participants: Mean age: Gender distribution: Inclusion criteria: Exclusion criteria: Recruitment Setting: Country:
Data collection	Definition of medication-related harm: Classification of severity: Classification of preventability: Data collection method and follow-up: Causality assessment:
Outcomes	Drop out/incomplete data:

	Incidence of MRH: Incidence by severity of MRH: Incidence by preventability of MRH: Number of patients experiencing MRH: Number of events: Type of MRH events (+ by system if applicable): Risk of MRH by drug class (frequency of events caused by one class) Reported risk factors for MRH
Dates of study	
Funding sources	
Additional Notes	

Adapted from Page AT, Clifford RM, Potter K, *et al*. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. *Br J Clin Pharmacol 2016;82:583-623*